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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,452	11/14/2003	R. Shoshana Bamdad Shendelman	M1015.70046US01	9378

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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,452	SHENDELMAN ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.000.

The undersigned Examiner supports the goal of the Office to advance prosecution as expediently as is reasonably possible. Cooperation is requested with respect to the timely submission of any references deemed pertinent to the present application along with Form PTO-1449.

Claims 1-4 are presented.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to the treatment of any invasive cancer, of any metastatic tumors, a human patient where angiogenesis inhibition is indication and a human patient wherein treatment with endostatin has been indicated. The specification fails to provide support for the claimed methods of treatment.

Attention is directed to In re Wands, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to methods of treatment of any invasive cancer, of any metastatic tumors, a human patient where angiogenesis inhibition is indication and a human patient wherein treatment with endostatin has been indicated.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the field of oncology.

Each particular neoplastic disease has its own specific characteristics and etiology. The broad recitations in each of the claims are inclusive of many conditions that presently have substantially no established successful therapies.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The breadth of the claims

The claims are very broad and inclusive of any invasive cancer and metastatic tumor, as well as various disorders wherein angiogenesis inhibition is indicated, or, treatment with endostatin is indicated.

The amount of direction or guidance provided and the presence or absence of working examples

There are no working examples specifically directed to an invasive cancer or a metastatic tumor wherein L-histidine, quisqualic acid or D-cycloserine is administered. There are no working examples specifically directed to a human patient who is treated with L-histidine, quisqualic acid or D-cycloserine where angiogenesis inhibition or treatment with endoststatin is indicated.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular invasive cancer or a metastatic tumor, or conditions where angiogenesis inhibition or treatment with endoststatin is indicated, is contemplated for treatment with L-histidine, quisqualic acid or D-cycloserine. The skilled artisan would expect the interaction of a particular compound in the treatment of a particular disease state to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding or any criteria for extrapolating beyond the laboratory determinations set forth in the specification. No direction is provided for any clinical application. Absent reasonable *a priori* expectations of success for using a particular chemotherapeutic agent to treat any invasive cancer or metastatic tumor or condition wherein angiogenesis inhibition is sought, one skilled in the oncology art would have to test extensively many disease states to discover which respond to a particular compound. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue

experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chugai Seiyaku Kabushiki Kaisha, GB 1,153,113.

The reference teaches the administration of cycloserine to decrease tumor activity in a laboratory model of Ehrlich ascites carcinoma, a malignant, invasive cancer derived from epithelial tissue that tends to metastasize to other areas of the body. See Example 1, page 3. Neither the D- nor L-form of cycloserine is disclosed. The reference does not disclose angiogenesis inhibition or treatment with endostatin. However, one skilled in the oncology art would have been motivated to seek the optimal form of cycloserine to treat an invasive cancer where susceptibility to metastasis exists. Both the D- and L-form of cycloserine are reasonably encompassed in the teaching. Angiogenesis, the development of blood vessels, is a requirement for tumor growth and dissemination. Endostatin is known in the prior art as an antiangiogenic agent. It would have been reasonable to expect where an agent is effective in treating an invasive cancer, and where the potential for metastasis is high, both angiogenesis inhibition and endostatin treatment would be indicated.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slusher et al., WO 97/48409.

Slusher teaches the administration of the NAALADase inhibitor, quisqualic acid, as a conformationally restricted glutamate mimic, to decrease the growth of LNCAP, a prostate cancer cell line. See Figure 1. Various metastatic tumors are encompassed in the teaching. See page 67, lines 18-19, and claim 7, pages 124-125. The reference does not disclose angiogenesis inhibition or treatment with endostatin. However, one skilled in the oncology art would have been motivated to inhibit angiogenesis and provide endostatin treatment in view of the state of the art. Such would have been obvious in the absence of evidence to the contrary because angiogenesis, the development of blood vessels, is a requirement for tumor growth and dissemination. Endostatin is known in the prior art as an antiangiogenic agent. It would have been reasonable to expect where an agent is effective in treating an invasive cancer, and where the potential for metastasis is high, both angiogenesis inhibition and endostatin treatment would be indicated.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached Mondays to Fridays from 10:30 AM to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Chris Low, can be reached at telephone

number 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis Spivack

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

June 26, 2005